Tony Pawson: In Memoriam

We lost a star scientist this summer, Tony Pawson, who made incredible contributions in his shortened career to our understanding of the biochemical mechanisms of cell signaling. Tony, a Canadian of British origin, performed groundbreaking research spanning nearly 40 years that provided tremendous insight into how biochemical signals communicate information both between and inside cells. He was the first to recognize that the transduction of these biochemical signals often involve strong noncovalent protein-protein interactions formed by highly conserved noncatalytic domain segments of signaling molecules, the prototype being the Src homology 2 "SH2" domain that he and graduate student Ivan Sadowski first coined back in the 1980s during early work on the oncogenic v-fps protein encoded by the Fujinami sarcoma virus (Sadowski et al., 1986). Tony subsequently demonstrated that these SH2 domains bound with high affinity to select phosphotyrosine-containing motifs in their target proteins, the first report being a landmark paper published in 1990 (Anderson et al., 1990). These crucial findings were rapidly confirmed and expanded upon by Tony's group and many other laboratories in the 1990s. The biological significance of the SH2 domain in neurobiology was first uncovered by Tony utilizing the power of *Drosophila* genetics. Here, graduate student Paul Olivier investigated how the small protein Drk (aka Grb2), consisting of only SH2 and SH3 domains and no inherent catalytic activity, could have such a profound effect on R7 photoreceptor cell development—and made the intriguing discovery that the sole function of this protein was to act as an "adaptor" molecule that connected the Sevenless receptor tyrosine kinase to Ras signaling inside of the cell (Olivier et al., 1993). Because of Tony's groundbreaking research on the SH2 domain, we all now understand that essential chemical signals initiated by catalytic proteins, such as tyrosine kinases and Ras-type GTPases, involves a complex array of protein-protein interactions mediated by distinct protein module "adaptor" domains that function to regulate signaling networks (Pawson, 1995). We now all take for granted the diverse group of protein-protein interaction modules like the SH2, SH3, PTB, 14-3-3, PDZ, WW, SAM, LIM, PH, and BAR domains that provide a central framework for how biochemical information is propagated. We must remember that Tony was the pioneer.

Though originally focused on cancer research, the ramifications of Tony's work spans all fields of biology and life sciences. You name it and his research findings impacted it, from embryology to immunology, cancer biology, and of course, neuroscience. Intrigued by axon guidance and the multitude of signals that must occur during this complicated biological process, Tony's laboratory probed the question with a series of biochemical, cellular, and genetic tests in mice focusing on the Eph family of receptor tyrosine kinases and their membrane-bound Ephrin ligands. Their findings changed the way we think about developmental neurobiology. They showed that Ephs, when stimulated by Ephrins, not only lead to signal transduction in the "receptor"-expressing cell but also activate signaling into the "ligand"-expressing cells—and this bidirectional signaling or cellular crosstalk is critical during the intricate process of guiding axons to their correct destinations (Henkemeyer et al., 1996). The idea that bidirectional cell-cell—or more precisely axon-cell—contact-mediated Eph-Ephrin interactions help instruct the wiring of the brain set the stage for our understanding how this large family of interacting receptors and ligands controls all sorts of cellular migration/adhesion-type events, including neuronal migration, synapse formation, and synaptic plasticity in the brain; the regulation of blood vessel growth throughout the body; midline development of the embryo; and of course stem cell biology.

Based on work from Tony's laboratory and others, new classes of drug discovery were enabled that ultimately led to the development of cell signaling modulators that treat disease—such as Gleevac, Nexavar, and Zelboraf. And while the SH2 domain and its biological function was his central discovery, he often ventured far away from his comfort zone and was able to tackle questions using myriad tools and model organisms he could get his hands on—from yeast to *C. elegans*, *Drosophila*, and *Mus musculus*—anything he could use to fulfill his desire to understand how cells communicate. His thirst for knowledge was never quenched, and we who had the chance to work in his laboratory got to see firsthand how excited and passionate his never-ending love of discovery was. Those who heard him on the lecture circuit and had the chance to interact with him during his travels got just a taste of his brilliance. He truly was an amazing person, with a gentle yet forceful ability to stimulate the minds of the many scientists he had trained and inspired. To quote three enduring words we and others surely remember coming from Tony's wonderful English accent when discussing an exciting new result or

Tony Pawson enjoying a family vacation in Greve, Tuscany. Photo contributed by his daughter, Catherine Pawson.

designing a cutting-edge experiment to answer an intriguing question, "I love it."

Rest in peace Tony.

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